

GOODMAN & GILMAN's The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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ANDROGENS

Peter J. Snyder

Testosterone is the principal circulating androgen in men. It is secreted by the Leydig cells of the testes in response to luteinizing hormone (LH) from the pituitary gland. The varied effects of testosterone are due to its ability to act by at least three different mechanisms: by binding to the androgen receptor; by conversion in certain tissues to dihydrotestosterone, which also binds to the androgen receptor; and by conversion to estradiol, which binds to the estrogen receptor. Testosterone is responsible for male sexual differentiation in utero and for male pubertal changes. Consequently, failure of a male fetus to secrete testosterone or to have functional androgen receptors during the first trimester results in incomplete male sexual differentiation; failure of testosterone secretion before puberty results in incomplete pubertal changes; and failure during adulthood results in a diminution, at different rates, of some aspects of virilization. In women the physiological role of testosterone and the consequences of its deficiency are not yet understood, but it is possible that it contributes to libido, energy, muscle mass and strength, and bone strength.

Oral administration of testosterone leads to absorption into the hepatic circulation but rapid catabolism by the liver, so oral ingestion is ineffective in delivering testosterone systemically. Most attempts to devise pharmacological testosterone preparations, therefore, have involved finding ways of bypassing hepatic catabolism. The 17 α -alkylated androgens can be administered orally and are not catabolized as rapidly as testosterone itself, but they tend to cause cholestasis. Esters of testosterone and a fatty acid, when injected, produce serum testosterone concentrations that remain within the normal range for one to several weeks. Transdermal preparations of testosterone deliver testosterone itself into the systemic circulation and, when applied daily, produce relatively even serum testosterone concentrations.

The major indication for testosterone treatment is male hypogonadism, for which a testosterone ester or transdermal preparation should be used. Treatment should be monitored for efficacy by measurement of the serum testosterone concentration and for deleterious effects by evaluating for obstruction to urine flow due to benign prostatic hyperplasia, for prostate cancer, and for erythrocytosis. Athletes have used androgens to attempt to improve their performance. Androgens have been used to attempt to develop a male contraceptive. For this purpose they have been used alone or in combination with a gonadotropin-releasing hormone (GnRH) antagonist or a progestin to suppress endogenous testosterone production and thereby spermatogenesis. The 17 α -alkylated androgens are used to treat angioneurotic edema, because they stimulate C1 esterase inhibitor. Some drugs are antiandrogens that are used intentionally to inhibit undesirable effects of androgens; other drugs, used for nonhormonal purposes, have side effects as a consequence of their antiandrogenic properties. Analogs of GnRH inhibit LH secretion and thereby reduce testosterone synthesis. They are used to treat metastatic prostate cancer. A side effect of the antifungal agents of the imidazole class (see Chapter 49) is direct inhibition of cortisol synthesis in the adrenal glands and testosterone synthesis in the testes. Flutamide and bicalutamide are androgen receptor antagonists that are used in combination with GnRH analogs in the treatment of metastatic prostate cancer because they block the effects of adrenal androgens. Spironolactone (see Chapter 29) is

an aldosterone receptor antagonist and also a weak androgen receptor antagonist that causes gynecomastia when used as a diuretic in men. Finasteride is an inhibitor of the 5 α -reductase enzyme, which is used to treat benign prostatic hyperplasia.

TESTOSTERONE AND OTHER ANDROGENS

Synthesis of Testosterone. In men, testosterone is the principal secreted androgen. The Leydig cells synthesize the majority of testosterone by the pathways shown in Figure 59-1. In women, testosterone also is probably the principal androgen and is synthesized both in the corpus luteum and the adrenal cortex by similar pathways. The testosterone precursors androstenedione and dehydroepiandrosterone are weak androgens.

Secretion and Transport of Testosterone. The magnitude of testosterone secretion is greater in men than in women at almost all stages of life, a difference that explains almost all other differences between men and women. In the first trimester *in utero*, the fetal testes begin

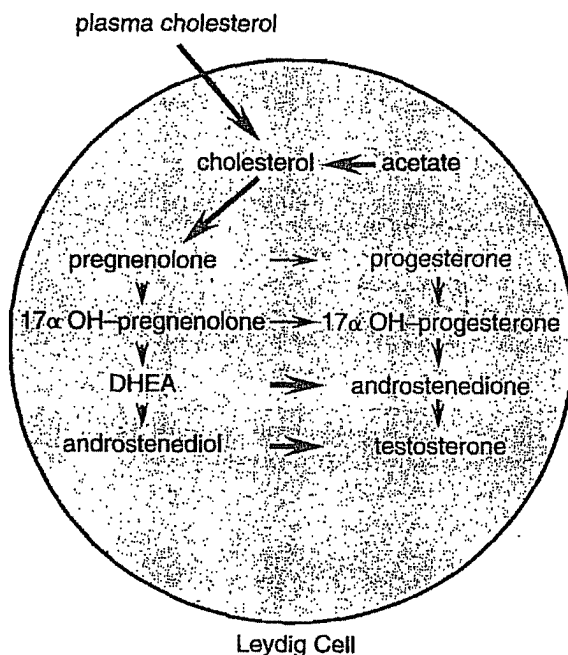


Figure 59-1. Pathway of synthesis of testosterone in the Leydig cells of the testes.

Bold arrows indicate favored pathways. DHEA, dehydroepiandrosterone. (Adapted from Santen, 1995, with permission.)

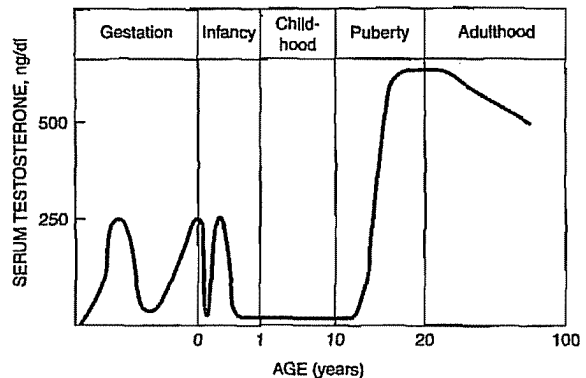


Figure 59-2. Schematic representation of the serum testosterone concentration from early gestation to old age.

to secrete testosterone, which is the principal factor in male sexual differentiation, probably stimulated by human chorionic gonadotropin from the placenta. By the beginning of the second trimester, the value is close to that of midpuberty, about 250 ng/dl (Figure 59-2) (Dawood and Saxena, 1977; Forest, 1975). Testosterone production then falls by the end of the second trimester, but by birth the value is again about 250 ng/dl (Forest and Cathiard, 1975; Forest, 1975; Dawood and Saxena, 1977), possibly due to stimulation of the fetal Leydig cells by luteinizing hormone (LH) from the fetal pituitary gland. The testosterone value falls again in the first few days after birth, but it rises and peaks again at about 250 ng/dl at two to three months after birth and falls to <50 ng/dl by six months, where it remains until puberty (Forest, 1975). During puberty, from about age 12 to 17 years, the serum testosterone concentration in males increases to a much greater degree than in females, so that by early adulthood the serum testosterone concentration is 500 to 700 ng/dl in men, compared to 30 to 50 ng/dl in women. The magnitude of the testosterone concentration in the male is responsible for the pubertal changes that further differentiate men from women. As men age, their serum testosterone concentrations gradually decrease, which may contribute to other effects of aging in men.

LH, secreted by the gonadotroph cells of the pituitary (see Chapter 56), is the principal stimulus of testosterone secretion in men, perhaps potentiated by follicle stimulating hormone (FSH), also secreted by the gonadotroph cells. GnRH from the hypothalamus (see Chapter 56), in

turn, stimulates LH secretion, and testosterone inhibits it, acting directly on the gonadotroph cell. LH is secreted in pulses, which occur approximately every two hours and are greater in magnitude in the morning. The pulsatility appears to result from pulsatile secretion of GnRH from the hypothalamus. Pulsatile administration of GnRH to men who are hypogonadal due to hypothalamic disease results in normal LH pulses and testosterone secretion, but continuous administration does not (Crowley *et al.*, 1985). Testosterone secretion is likewise pulsatile and diurnal, with the highest plasma concentrations occurring at about 8 A.M. and the lowest at about 8 P.M. The morning peaks diminish as men age (Bremner *et al.*, 1983).

In women, LH stimulates the corpus luteum (formed from the follicle after release of the ovum) to secrete testosterone. Under normal circumstances, however, estradiol and progesterone, not testosterone, are the principal inhibitors of LH secretion in women. Sex hormone binding globulin (SHBG) binds about 40% of circulating testosterone with high affinity. Albumin binds almost 60% of circulating testosterone with low affinity. Approximately 2% of testosterone is unbound or free.

Metabolism of Testosterone to Active and Inactive Compounds. Testosterone has many different effects in many different tissues. One of the mechanisms by which the varied effects are mediated is the metabolism of testosterone to two other active steroids, dihydrotestosterone and estradiol (Figure 59-3). Some effects of testosterone

appear to be mediated by testosterone itself, some by dihydrotestosterone, and some by estradiol.

The enzyme 5 α -reductase irreversibly catalyzes the conversion of testosterone to dihydrotestosterone. Although both testosterone and dihydrotestosterone act *via* the same receptor, the androgen receptor, dihydrotestosterone binds with higher affinity (Wilbert *et al.*, 1983) and activates gene expression more efficiently (Deslypere *et al.*, 1992). As a result, testosterone, acting *via* dihydrotestosterone, is able to have effects in tissues that express 5 α -reductase which it could not have if it were present only as testosterone. Two forms of 5 α -reductase have been identified: type I, which is found predominantly in nongenital skin and the liver, and type II, which is found predominantly in urogenital tissue in men and genital skin in both men and women. The effects of dihydrotestosterone in these tissues are described below.

The enzyme complex aromatase, which is present in many tissues, especially the liver and adipose tissue, catalyzes the irreversible conversion of testosterone to estradiol. This conversion results in approximately 85% of circulating estradiol in men; the remainder is secreted directly by the testes, probably the Leydig cells (MacDonald *et al.*, 1979). The effects of testosterone thought to be mediated *via* estradiol are described below.

Testosterone is metabolized in the liver to androsterone and etiocholanolone (Figure 59-3), which are biologically inactive. Dihydrotestosterone is metabolized to androsterone, androstanedione, and androstanediol.

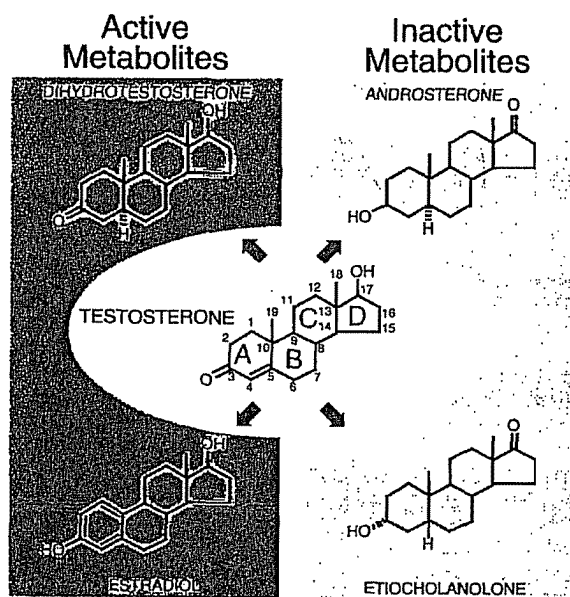


Figure 59-3. Metabolism of testosterone to its major active and inactive metabolites.

Physiological and Pharmacological Effects of Androgens

The biological effects of testosterone can be considered by the mechanisms by which they occur and by the tissues in which they occur at various stages of life. Testosterone can act as an androgen either directly by binding to the androgen receptor or indirectly by conversion to dihydrotestosterone, which also binds to the androgen receptor as described above. Testosterone also can act as an estrogen by conversion to estradiol, which binds to the estrogen receptor (Figure 59-4).

Effects That Occur *via* the Androgen Receptor. Testosterone and dihydrotestosterone both act as androgens *via* a single androgen receptor (Figure 59-5). The androgen receptor is a member of the superfamily of nuclear receptors, which includes steroid hormone receptors, thyroid hormone receptors, and orphan receptors (*see* Chapter 2). Both testosterone and dihydrotestosterone bind to the hormone-binding domain of the androgen receptor,

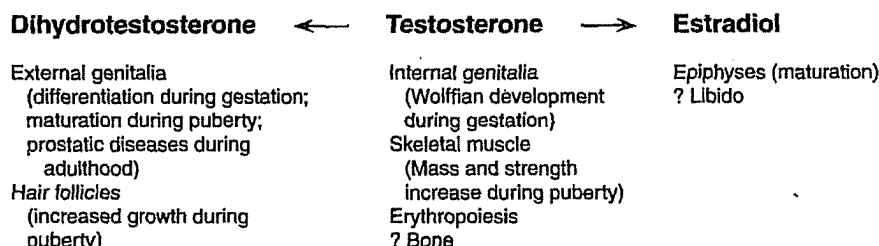


Figure 59-4. Direct effects of testosterone and effects mediated indirectly via dihydrotestosterone or estradiol.

allowing the ligand-receptor complex to bind, via the DNA-binding domain of the receptor, to certain responsive genes. The ligand-receptor complex acts as a transcription factor complex and stimulates expression of those genes (Brinkmann and Trapman, 2000).

For many years, the mechanisms by which androgens had so many different actions in so many different tissues were not understood, but recently these mechanisms have become clearer. One mechanism is the higher affinity with which dihydrotestosterone binds to and activates the androgen receptor compared to testosterone (Deslypere *et al.*, 1992; Wilbert *et al.*, 1983). Another mechanism, postulated more recently, involves transcription cofactors, both coactivators and corepressors, that are tissue specific.

The importance of the androgen receptor is illustrated by the consequences of its mutations. Predictably, mutations that either alter the primary sequence of the protein or cause a single amino acid substitution in the hormone- or DNA-binding domains result in resistance to the action of testosterone, beginning *in utero* (McPhaul and Griffin, 1999). Male sexual differentiation is, therefore, incomplete, as is pubertal development.

Another kind of mutation occurs in patients who have spinal and bulbar muscular atrophy, known as Kennedy's disease. These patients have an expansion of the CAG repeat, which codes for glutamine, at the amino terminus of the molecule (Laspada *et al.*, 1991). The result is very mild androgen resistance but progressively severe motor neuron atrophy. The mechanism by which the neuron atrophy occurs is unknown.

Yet other kinds of androgen receptor mutations may explain why prostate cancer that is treated by androgen deprivation eventually becomes androgen-independent. Prostate cancer is initially at least partially androgen-sensitive, which is the basis for the initial treatment of metastatic prostate cancer by

androgen deprivation. Metastatic prostate cancer often regresses initially in response to this treatment, but then becomes unresponsive to continued deprivation. Several mutations of the androgen receptor have been described in these patients, and it has been postulated that these mutations might allow the receptor to respond to ligands other than androgens or to act without ligand activation (Visakorpi *et al.*, 1995).

Effects That Occur via the Estrogen Receptor. The effects of testosterone on at least one tissue are mediated by its conversion to estradiol, catalyzed by the aromatase enzyme complex. In the rare cases in which a male does not express aromatase (Carani *et al.*, 1997; Morishima *et al.*, 1995) or the estrogen receptor (Smith *et al.*, 1994), the epiphyses do not fuse and long bone growth continues indefinitely. In addition, the patients are osteoporotic. Administration of estradiol corrects the bone abnormalities in patients with an aromatase defect (Bilezikian *et al.*, 1998) but not an estrogen-receptor defect. There is evidence suggesting that conversion of testosterone to estradiol mediates male sexual behavior in rats, but similar evidence has not yet been found in human beings.

Effects of Androgens at Different Stages of Life. In Utero. When the fetal testes, stimulated by human chorionic gonadotropin, begin to secrete testosterone at about the eighth week of gestation, the high local concentration of testosterone around the testes stimulates the nearby Wolffian ducts to differentiate into the male internal genitalia: the epididymis, vas deferens, and seminal vesicles (George and Wilson, 1992). Further away, in the anlage of the external genitalia, testosterone is converted to dihydrotestosterone, which causes the development of the external genitalia: the penis, scrotum, and prostate (George and Wilson, 1992). The increase in testosterone at the end of gestation might result in further phallic growth.

Infancy. The consequences of the increase in testosterone secretion by the testes during the first few months of life are not yet known.

Puberty. Puberty in the male begins at a mean age of 12 years with an increase in the secretion of FSH and LH from the gonadotroph cells, stimulated by increased secretion of GnRH from the hypothalamus. The increased secretion of FSH and LH stimulate the testes, so, not surprisingly, the first sign of

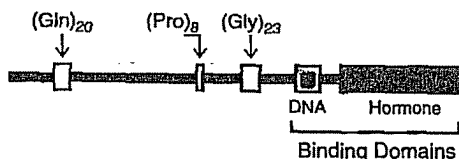


Figure 59-5. Structure of the androgen receptor.

puberty is an increase in testicular size. The increase in testosterone production within the testes, along with the effect of FSH on the Sertoli cells, stimulates the development of the seminiferous tubules, which eventually produce mature sperm. Increased secretion of testosterone into the systemic circulation affects many tissues virtually simultaneously, and the changes in most of them occur gradually during the course of several years. The phallus enlarges in length and width, the scrotum becomes rugated, and the prostate begins secreting the fluid it contributes to the semen. The skin becomes coarser and oilier due to increased sebum production, which contributes to the development of acne. Sexual hair begins to grow, initially pubic and axillary hair, then hair on the lower legs, and finally other body hair and facial hair. Full development of the latter two may not occur until ten years after the start of puberty and marks the completion of puberty. Muscle mass and strength, especially of the shoulder girdle, increase, and subcutaneous fat decreases. Epiphyseal bone growth accelerates, resulting in the pubertal growth spurt, but epiphyseal maturation leads eventually to a slowing and then cessation of growth. Bone also becomes thicker. The increase in muscle mass and bone result in a pronounced increase in weight. Erythropoiesis increases, resulting in higher hematocrit and hemoglobin concentrations in men than boys or women. The larynx thickens, resulting in a lower voice. Libido develops.

Other changes also may be the result of the increase in testosterone during puberty. Men tend to have a better sense of spatial relations than do women and to exhibit behavior that is different in some ways from that of women, including being more aggressive.

Adulthood. The serum testosterone concentration and the characteristics of the adult male are maintained largely during early adulthood and midlife. One change during this time is the gradual development of male pattern baldness, beginning with recession of hair at the temples and/or at the vertex.

Two changes that can occur in the prostate gland during adulthood are of much greater medical significance. One is the gradual development of benign prostatic hyperplasia, which occurs to a variable degree in almost all men, sometimes to the degree of obstructing urine outflow by compressing the urethra as it passes through the prostate. This development is mediated by the conversion of testosterone to dihydrotestosterone within prostatic cells (Wilson, 1980). One current treatment of benign prostatic hyperplasia is based on inhibiting 5 α -reductase II, which mediates this conversion (McConnell *et al.*, 1998), as discussed below.

The other change that can occur in the prostate during adulthood is the development of cancer. Although no direct evidence suggests that testosterone causes the disease, prostate cancer is dependent on testosterone, at least to some degree and at some time in its course. This dependency is the basis of treating metastatic prostate cancer by lowering the serum testosterone concentration (Huggins and Hodges, 1941; Iversen *et al.*, 1990).

Senescence. As men age, the serum testosterone concentration gradually declines (Figure 59-2) and the sex hormone-binding globulin concentration gradually increases, so that by age 80, the total testosterone concentration is approximately 85% and the free testosterone is approximately 40% of those at age 20 (Purifoy *et al.*, 1981; Deslypere and Vermeulen, 1984). This fall in serum testosterone could contribute to several other changes

that occur with increasing age in men, including decreases in energy, libido, muscle mass (Forbes, 1976) and strength (Murray *et al.*, 1980), and bone mineral density (Riggs *et al.*, 1982). The possibility of such a relationship is suggested by the occurrence of similar changes when men develop hypogonadism at a younger age due to known diseases, as discussed below.

Consequences of Androgen Deficiency

The consequences of androgen deficiency depend on the stage of life during which the deficiency first occurs and the degree of the deficiency.

During Fetal Development. Testosterone deficiency in a male fetus during the first trimester *in utero* causes incomplete sexual differentiation. Testosterone deficiency in the first trimester results only from testicular disease, such as deficiency of 17 α -oxidoketoreductase; deficiency of LH secretion due to pituitary or hypothalamic deficiency does not result in testosterone deficiency during the first trimester, because Leydig-cell secretion of testosterone at that time is under the control of hCG from the placenta. Complete deficiency of testosterone secretion results in entirely female external genitalia; less severe testosterone deficiency results in incomplete virilization of the external genitalia proportionate to the degree of deficiency. Testosterone deficiency at this stage of development also leads to failure of the Wolffian ducts to differentiate into the male external genitalia, such as the vas deferens and seminal vesicles, but the müllerian ducts do not differentiate into the female external genitalia as long as testes are present and secrete müllerian inhibitory substance. Similar changes occur if testosterone is secreted normally, but its action is diminished because of an abnormality of the androgen receptor or of the 5 α -reductase enzyme. Abnormalities of the androgen receptor can be quite variable. The most severe form results in complete absence of androgen action and a female phenotype; moderately severe forms result in partial virilization of the external genitalia; and the mildest forms permit normal virilization *in utero* and result only in impaired spermatogenesis in adulthood (McPhaul and Griffin, 1999). Abnormal 5 α -reductase results in incomplete virilization of the external genitalia *in utero* but normal development of the male internal genitalia, which depends on testosterone *per se* (Wilson *et al.*, 1993).

Testosterone deficiency during the third trimester, due either to a testicular disease or a deficiency of fetal LH secretion, appears to have two known consequences. One is failure of the phallus to grow as much as it would normally. The result, called micropallus, is a common occurrence in boys later discovered to be unable to secrete

LH due to abnormalities of GnRH synthesis. The other consequence is failure of the testes to descend into the scrotum, called cryptorchidism, also a common occurrence in boys whose LH secretion is subnormal.

Before Completion of Puberty. When a boy can secrete testosterone normally *in utero* but loses the ability to do so before the anticipated age of puberty, the result is failure to complete puberty. All of the pubertal changes described above, including those of the external genitalia, sexual hair, muscle mass, voice, and behavior, fail to occur to a degree proportionate to the abnormality of testosterone secretion. In addition, if growth hormone secretion is normal when testosterone secretion is subnormal during the years of expected puberty, the long bones continue to lengthen because the epiphyses do not close. The result is longer arms and legs relative to the trunk; these proportions are referred to as eunuchoid. Another consequence of subnormal testosterone secretion during the age of expected puberty is enlargement of glandular breast tissue, called gynecomastia.

After Completion of Puberty. When the ability to secrete testosterone becomes impaired after the completion of puberty, regression of the pubertal effects of testosterone depends on both the degree and the duration of testosterone deficiency. When the degree of testosterone deficiency is substantial, libido and energy decrease within a week or two, but other testosterone-dependent characteristics decline more slowly. Decreases in muscle mass and strength probably can be detected by testing groups of men within a few months, but a clinically detectable decrease in muscle mass in an individual does not occur for several years. A pronounced decrease in hematocrit and hemoglobin will occur within several months. A decrease in bone mineral density probably can be detected by dual energy absorptiometry within two years, but an increase in fracture incidence likely would not occur for many years. A loss of sexual hair takes many years.

In Women. Loss of androgen secretion in women results in a decrease in sexual hair, but not for many years. Androgens may have other important effects in women, and the loss of androgens (especially severe loss of both ovarian and adrenal androgens, as occurs in panhypopituitarism) may result in the loss of these effects. Testosterone preparations that can yield serum testosterone concentrations in the physiological range in women currently are being developed. The availability of such preparations will allow determining if replacement of testosterone in androgen-deficient women will improve their libido, energy, muscle mass and strength, and bone mineral density.

Therapeutic Androgen Preparations

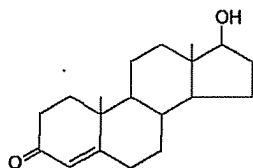
The need for a creative approach to pharmacotherapy with androgens arises from the fact that ingestion of testosterone is not an effective means of replacing testosterone deficiency. The reason is that, even though ingested testosterone is readily absorbed into the hepatic circulation, the hormone is catabolized so rapidly by the liver that it is not practical for a hypogonadal man to ingest it in sufficient amounts and with sufficient frequency to maintain a normal serum testosterone concentration. Most pharmaceutical preparations of androgens, therefore, are designed to bypass hepatic catabolism of testosterone. Another goal of androgen pharmacotherapy is to separate certain effects from others.

Testosterone Esters. Esterifying a fatty acid to the 17 β hydroxyl group of testosterone creates a compound that is even more lipophilic than testosterone itself. When an ester, such as *testosterone enanthate* (heptanoate) or *cypionate* (cyclopentylpropionate) (Figure 59-6) is dissolved in oil and administered intramuscularly every two to four weeks to hypogonadal men, the ester hydrolyzes *in vivo* and results in serum testosterone concentrations that range from higher than normal in the first few days after the injection to low-normal just before the next injection (Snyder and Lawrence, 1980; Figure 59-7). Attempts to decrease the frequency of injections by increasing the amount of each injection result in wider fluctuations and poorer therapeutic effects. The undecanoate ester of testosterone (Figure 59-6), when dissolved in oil and ingested orally, is absorbed into the lymphatic circulation, thus bypassing initial hepatic catabolism. *Testosterone undecanoate* in oil also can be injected and produces stable serum testosterone concentrations for a month (Zhang *et al.*, 1998). The undecanoate ester of testosterone is not marketed in the United States.

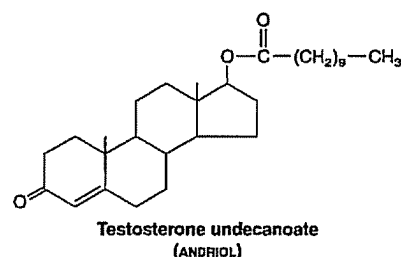
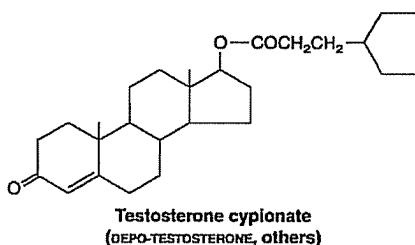
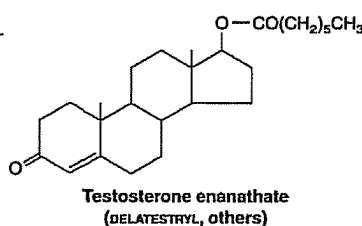
Alkylated Androgens. Several decades ago, chemists found that adding an alkyl group to the 17 α position of testosterone (Figure 59-6) retarded hepatic catabolism of the molecule. Consequently, 17 α -alkylated androgens do have an androgenic effect when administered orally. However, they do not appear to be as fully androgenic as testosterone itself, and they cause hepatotoxicity (Peters *et al.*, 1962; Cabasso, 1994), whereas native testosterone does not.

Transdermal Delivery Systems. Recent attempts to avoid the destructive "first pass" of testosterone through the liver have employed novel delivery systems, instead

Testosterone (HISTERONE, others)



Testosterone Esters



17 α -Alkylated Androgens

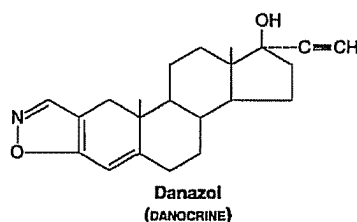
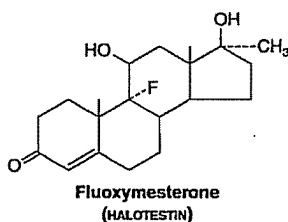
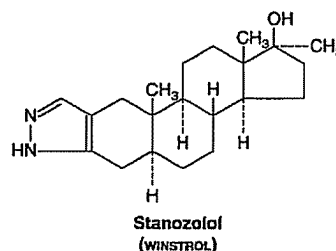
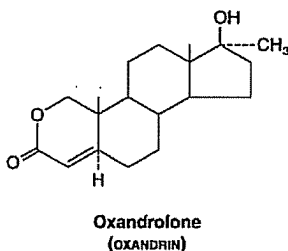
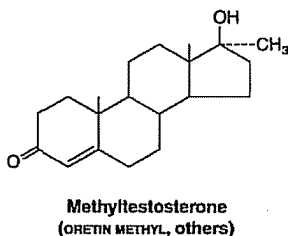


Figure 59-6. Structures of androgens available for therapeutic use.

of chemically modified testosterone, that release native testosterone across the skin in a controlled fashion. When these transdermal preparations are applied once a day, they result in serum testosterone concentrations that fluctuate less than when testosterone esters are administered systemically. The first such preparation was a skin patch (TESTODERM) designed to be applied to the scrotal skin (Findlay *et al.*, 1989). The rationale for that location is that the scrotal skin is so thin that sufficient testosterone can be absorbed without the need for chemicals to facil-

itate its absorption. Subsequent patches were designed to be applied to nonscrotal skin (ANDRODERM, TESTODERM TTS) and therefore employ chemicals to facilitate absorption (Yu *et al.*, 1997; Dobs *et al.*, 1999). A newer transdermal preparation (ANDROGEL) employs a hydroalcoholic gel which is applied to nonscrotal skin (Wang *et al.*, 2000). All of these preparations are applied once a day, and all produce serum testosterone concentrations within the normal range in the majority of hypogonadal men (Figure 59-7).

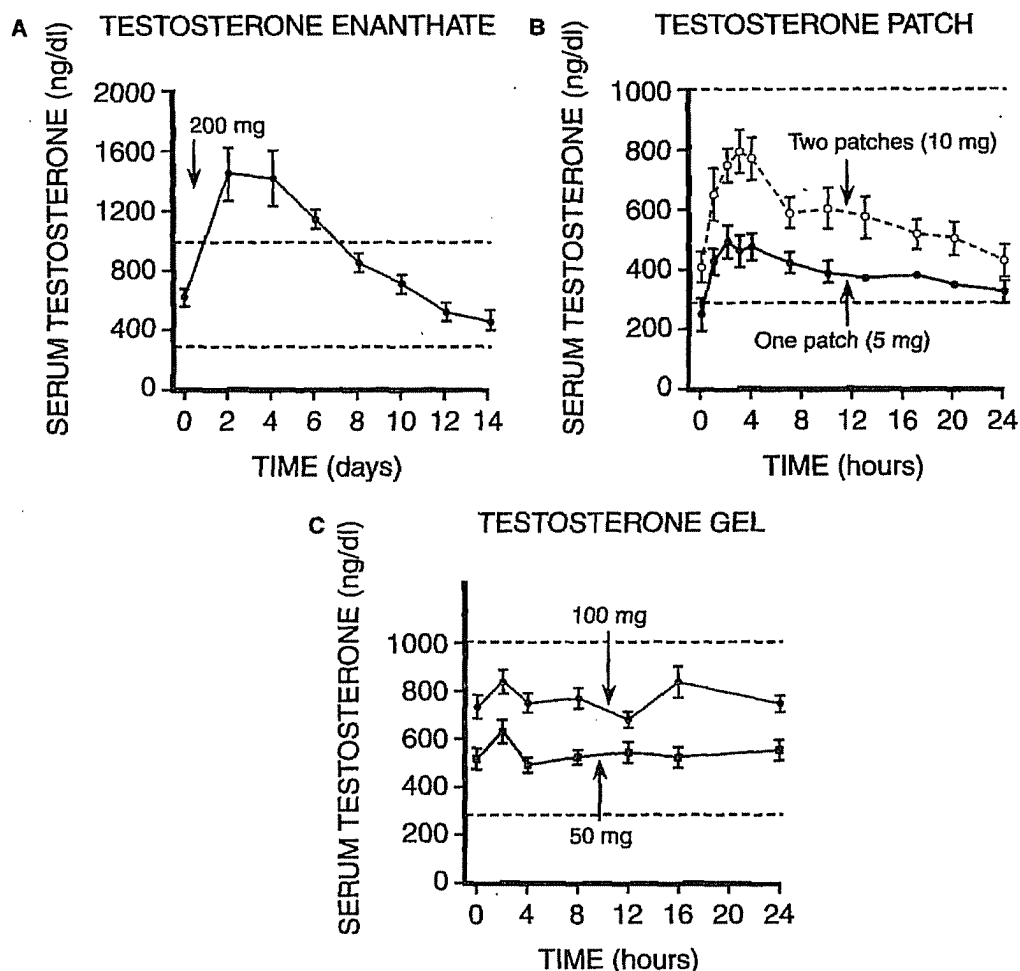


Figure 59-7. Pharmacokinetic profiles of three testosterone preparations during their chronic administration to hypogonadal men.

Doses of each were given at time 0. [Adapted from Snyder and Lawrence (1980) (A); Yu *et al.* (1997) (B); and Wang *et al.* (2000) (C).] Dashed lines indicate range of normal levels.

Attempts to Design Selective Androgens

Alkylated Androgens. Decades ago, investigators attempted to synthesize analogs of testosterone that possessed greater anabolic effects than androgenic effects compared to native testosterone. Several compounds appeared to have such differential effects, based on a greater effect on the levator ani muscle compared to the ventral prostate of the rat (Hershberger and Meyer, 1953). These compounds were called anabolic steroids, and most are 17α -alkylated androgens, described above. None of these compounds, however, has been demonstrated to have such

a differential effect in human beings. Nonetheless, they have enjoyed popularity among athletes who are attempting to improve their performance, as described below. Another alkylated androgen, 7α -methyl-19-nortestosterone, is poorly converted to dihydrotestosterone (Kumar *et al.*, 1992).

Selective Androgen-Receptor Modulators. Stimulated by the development of selective estrogen-receptor modulators, which have estrogenic effects in some tissues but not others, investigators are now attempting to develop selective androgen-receptor modulators (Negro-Vilar, 1999). However, the selective effect of *raloxifene* (EVISTA), the first estrogen-receptor modulator to be developed for clinical use, derives from its much greater

affinity for the form of estrogen receptor expressed in certain tissues, such as bone and cardiac muscle, than for the form expressed in other tissues, such as breast and uterus. Because only one form of the androgen receptor is expressed, development of compounds that have certain androgen effects but not others is based, instead, on tissue specificity of coactivators and corepressors of androgen-receptor transcriptional activity. Endogenous protein coactivators and corepressors of androgen receptor-dependent transcription have been demonstrated (Moilanen *et al.*, 1999), and a family of quinolinones that has selective androgen properties has been synthesized (Zhi *et al.*, 1999).

Therapeutic Uses of Androgens

The clearest indication for administration of androgens is testosterone deficiency in men, *i.e.*, treatment of male hypogonadism. Androgens also have been used in other situations in the past and likely will be used in yet others in the future.

Male Hypogonadism. Any of the transdermal testosterone preparations or testosterone esters described above can be used to treat testosterone deficiency. Monitoring treatment for beneficial and deleterious effects differs somewhat in adolescents and the elderly from that in other men.

Monitoring for Efficacy. The goal of administering testosterone to a hypogonadal man is to mimic the normal serum concentration as closely as possible. Therefore, measuring the serum testosterone concentration during treatment is the most important aspect of monitoring testosterone treatment for efficacy. When the serum testosterone concentration is measured depends on the testosterone preparation used. When a transdermal preparation is used, the serum testosterone concentration can be measured on any day at any time, recognizing that, when a patch is used, the peak value will be found 2 to 4 hours after application of the patch for scrotal skin (Findlay *et al.*, 1987), 2 to 4 hours after application of one patch for nonscrotal skin (TESTODERM TTS; Yu *et al.*, 1997), and 6 to 9 hours after application of another patch for nonscrotal skin (ANDRODERM; Dobs *et al.*, 1999). The nadir, before the next application, will be about 60% to 70% of the peak value (Findlay *et al.*, 1987). When the testosterone gel is used, there is no appreciable fluctuation during the course of the day, but steady-state values may not be reached for a month after the initiation of treatment. When the enanthate or cypionate esters of testosterone are administered once every two weeks, the serum testosterone concentration should be measured midway between doses. At each of these times, the serum testosterone concentration should be normal, and if not, the dosage schedule should be adjusted accordingly. If the cause of the testosterone deficiency is testicular disease, as indicated by an elevated serum LH concentration, adequacy of testosterone treatment also can be judged by its reduction to normal within two months of initiation of treatment (Snyder and Lawrence, 1980; Findlay *et al.*, 1989).

Normalization of the serum testosterone concentration results in normal virilization in men who are not normally virilized

and maintenance of virilization in those who already are. Libido and energy in hypogonadal men should increase within a few weeks (Davidson *et al.*, 1979). Muscle mass should increase, fat mass should decrease, and muscle strength should increase within a few months (Katznelson *et al.*, 1996). Bone mineral density should increase to a maximum within two years (Snyder *et al.*, 2000).

Monitoring for Deleterious Effects. When testosterone itself is administered, as in one of the transdermal preparations or as an ester that is hydrolyzed to testosterone (Caminos-Torres *et al.*, 1977), it has no "side effects" *i.e.*, no effects that endogenously secreted testosterone does not have, as long as the dose is not excessive. Modified testosterone compounds, such as the 17 α -alkylated androgens, do have side effects. Even replacement of endogenously secreted testosterone levels, however, can have effects that are undesirable. Some effects occur shortly after testosterone administration is initiated, whereas others usually do not occur until administration has been continued for many years. Raising the serum testosterone concentration from prepubertal or midpubertal levels to that of an adult male at any age can result in undesirable effects similar to those that occur during puberty, including acne, gynecomastia, and more aggressive sexual behavior. Physiological amounts of testosterone do not appear to affect serum lipids or apolipoproteins. Replacement of physiological levels of testosterone occasionally may have undesirable effects in the presence of concomitant illnesses. For example, stimulation of erythropoiesis would increase the hematocrit from subnormal to normal in a healthy man, but would raise the hematocrit above normal in a man with a predisposition to erythrocytosis, such as in chronic pulmonary disease. Similarly, the mild degree of sodium and water retention with testosterone replacement would have no clinical effect in a healthy man but would exacerbate preexisting congestive heart failure. If the testosterone dose is excessive, erythrocytosis and, uncommonly, salt and water retention and peripheral edema occur even in men who have no predisposition to these conditions. When a man's serum testosterone concentration has been in the normal adult male range for many years, whether from endogenous secretion or exogenous administration, and he is over age 40, he is subject to certain testosterone-dependent diseases, including benign prostatic hyperplasia and prostate cancer, as discussed above.

The principal side effects of the 17 α -alkylated androgens are hepatic, including cholestasis and, uncommonly, peliosis hepatis, blood-filled hepatic cysts. Hepatocellular cancer has been reported rarely, so that an etiologic link is uncertain. The 17 α -alkylated androgens, especially in large amounts, may lower serum high-density-lipoprotein cholesterol.

Monitoring at the Anticipated Time of Puberty. Administration of testosterone to testosterone-deficient boys at the anticipated time of puberty should be guided by the considerations above, but also by the fact that testosterone accelerates epiphyseal maturation, leading initially to a growth spurt but then to epiphyseal closure and permanent cessation of linear growth. Consequently, the height and growth-hormone status of the boy must be considered. Boys who are short because of growth-hormone deficiency

should be treated with growth hormone before their hypogonadism is treated with testosterone.

Male Senescence. Preliminary evidence suggests that increasing the serum testosterone concentration of men whose serum levels are subnormal for no reason other than their age will increase their bone mineral density and lean mass and decrease their fat mass (Snyder *et al.*, 1999a; Snyder *et al.*, 1999b). It is entirely uncertain at this time, however, if such treatment will worsen benign prostatic hyperplasia or increase the incidence of clinically detectable prostate cancer.

Female Hypogonadism. It remains to be determined if increasing the serum testosterone concentrations of women whose serum testosterone concentrations are below normal will improve their libido, energy, muscle mass and strength, and bone mineral density.

Enhancement of Athletic Performance. Some athletes take drugs, including androgens, to attempt to improve their performance. Because androgens taken for this purpose usually are taken surreptitiously, information about their possible effects is not as good as that for androgens taken for treatment of male hypogonadism.

Kinds of Androgens Used. Virtually all androgens produced for human or veterinary purposes have been taken by athletes. When use by athletes began more than two decades ago, 17 α -alkylated androgens and other compounds that were thought to have greater anabolic effects than androgen effects relative to testosterone (so-called "anabolic steroids") were used most commonly. Because these compounds can be detected readily by organizations that govern athletic competitions, preparations that increase the serum concentration of testosterone itself, such as the testosterone esters or human chorionic gonadotropin, have increased in popularity. Testosterone precursors, such as androstenedione and dehydroepiandrosterone (DHEA), also have increased in popularity recently because they are not regulated by national governments or athletic organizations.

Efficacy. Most studies of the effects of pharmacological doses of androgens on muscle strength have been uncontrolled, but in one study, testosterone or placebo was administered in a double-blind fashion. In that study, 43 men were randomized to one of four groups: strength training exercise with either 600 mg of testosterone enanthate once a week (more than six times a replacement dose) or placebo for testosterone; or no exercise with either testosterone or placebo. The men who received testosterone experienced an increase in fat-free mass and muscle strength compared to those who received placebo treatment, and the men who exercised simultaneously experienced even greater increases (Bhasin *et al.*, 1997).

In another double-blind study, men who took 100 mg of androstenedione three times a day for eight weeks did not experience an increase in muscle strength compared to men who took placebo. Failure of this treatment to increase muscle strength is

not surprising, because it also did not increase the mean serum testosterone concentration (King *et al.*, 1999).

Side Effects. Some side effects of taking pharmacological doses of androgens occur with all androgens and all circumstances, but others occur only with certain androgens or in certain circumstances. All androgens suppress gonadotropin secretion when taken in high doses and thereby suppress endogenous testicular function. The result is a decrease in both endogenous testosterone and sperm production, resulting in diminished fertility. If administration continues for many years, testicular size may diminish. Testosterone and sperm production usually return to normal within a few months of discontinuation but may take longer. High doses of androgens also causes erythrocytosis (Drinka *et al.*, 1995).

Androgens that can be converted to estrogens, such as testosterone itself, cause gynecomastia when administered in high doses. Androgens whose A ring has been modified so that it cannot be aromatized, such as dihydrotestosterone, do not cause gynecomastia even in high doses.

The 17 α -alkylated androgens are the only androgens that cause hepatotoxicity, as discussed above. These androgens also appear to be much more likely than others, when administered in high doses, to affect serum lipid concentrations, specifically to decrease high-density-lipoprotein (HDL) cholesterol and increase low-density-lipoprotein (LDL) cholesterol. Other side effects have been suggested by many anecdotes but have not been confirmed, including psychological disorders and sudden death due to cardiac disease, possibly related to changes in lipids or to coagulation activation.

Certain side effects occur specifically in women and children. Both experience virilization, including facial and body hirsutism, temporal hair recession in a male pattern, and acne. Boys experience phallic enlargement and women clitoral enlargement. Boys and girls whose epiphyses have not yet closed experience premature closure and stunting of linear growth.

Male Contraception. Attempts currently are being made to develop androgens alone or in combination with other drugs as male contraceptives based on their ability to inhibit secretion of LH by the pituitary, which in turn decreases endogenous testosterone production. Because the concentration of testosterone within the testes is normally approximately one hundred times that in the peripheral circulation, and that concentration is necessary for spermatogenesis, suppression of endogenous testosterone production greatly diminishes spermatogenesis. Initial use of testosterone alone to suppress spermatogenesis, however, required administration of approximately twice as much testosterone enanthate as would be used for physiological replacement, and even then spermatogenesis was not entirely suppressed in all men (WHO Task Force for the Regulation of Male Fertility, 1996). Other early attempts to suppress spermatogenesis employed a GnRH antagonist to suppress LH secretion combined with a physiological dose of testosterone to maintain a normal serum testosterone concentration (Pavlou *et al.*, 1991). That combination is not practical for widespread use because existing GnRH antagonists require daily injection and have strong histamine-releasing properties. A more promising approach is the combination of a progestin with a physiological dose of testosterone to suppress LH secretion and spermatogenesis but provide a normal serum testosterone concentration (Bebb *et al.*, 1996). Androgens currently being tested as part of male

contraceptive regimens include an injectable form of testosterone undecanoate, which appears to produce a relatively stable serum testosterone concentration for a month (Zhang *et al.*, 1999), and 7 α -methyl-19-nortestosterone, a synthetic androgen that cannot be metabolized to dihydrotestosterone (Cummings *et al.*, 1998).

Catabolic and Wasting States. Testosterone, because of its anabolic effects, has been used in attempts to ameliorate catabolic and muscle-wasting states, but it has not been effective in most of these states. One exception is in the treatment of muscle wasting associated with acquired immunodeficiency syndrome (AIDS), which is accompanied by hypogonadism. Treatment of men with AIDS-related muscle wasting and subnormal serum testosterone concentrations increases their muscle mass and strength (Bhasin *et al.*, 2000).

Angioneurotic Edema. Chronic androgen treatment of patients with angioneurotic edema effectively prevents attacks. The disease is caused by hereditary impairment of C1-esterase inhibitor or acquired development of antibodies against it (Cicardi *et al.*, 1998). The 17 α -alkylated androgens, such as stanozolol and danazol, act by stimulating the hepatic synthesis of the esterase inhibitor. In women, virilization is a potential side effect. In children virilization and premature epiphyseal closure prevent chronic use of androgens for prophylaxis, although they are used occasionally for treatment of acute episodes.

Blood Dyscrasias. Androgens once were employed to attempt to stimulate erythropoiesis in patients with anemias of various etiologies, but the availability of erythropoietin has supplanted that use. Androgens, such as danazol, still are used occasionally as adjunctive treatment for hemolytic anemia and idiopathic thrombocytopenic purpura that are refractory to first-line agents.

ANTIANDROGENS

Because certain effects of androgens are undesirable, at least under certain circumstances, agents have been developed specifically to inhibit androgen synthesis or effects. Other drugs, originally developed for other purposes, have been found to be antiandrogens. When these drugs are used for their originally intended purposes, their antiandrogenic effects can be undesirable side effects, but some are used intentionally as antiandrogens.

Inhibitors of Testosterone Synthesis. Analogs of GnRH effectively inhibit testosterone synthesis by inhibiting LH secretion. GnRH antagonists block the action of endogenous GnRH at the gonadotroph cell's GnRH receptor. Antagonists that are currently available require daily injection and have significant histamine-releasing properties, so their therapeutic use is not practical. GnRH "superactive" analogs, given repeatedly, down-regulate the GnRH receptor, and currently are available for treatment of metastatic prostate cancer (*see* Chapter 56).

Some antifungal drugs of the imidazole family, such as ketoconazole (*see* Chapter 49), block the synthesis of steroids, including testosterone and cortisol (Feldman, 1986). Because of the inhibition of cortisol and hepatotoxicity, these drugs are not generally useful to inhibit androgen synthesis intentionally.

Inhibitors of Androgen Action

These drugs act by inhibiting the binding of androgens to the androgen receptor or by inhibiting 5 α -reductase.

Androgen Receptor Antagonists. *Flutamide and Bicalutamide.* These are relatively potent androgen receptor antagonists which are limited in their effectiveness when used alone, because increased secretion of LH stimulates higher serum testosterone concentrations. They are used primarily in conjunction with a GnRH analog in the treatment of metastatic prostate cancer (*see* Chapter 52). In this situation, they block the action of adrenal androgens, which are not inhibited by GnRH analogs. Survival rates in groups of patients with metastatic prostate cancer treated with a combination of a GnRH agonist and either flutamide (EVLEXIN) or bicalutamide (CASODEX) are similar to each other (Schellhammer, Sharifi, *et al.*, 1995) and to survival rates in those treated by castration (Iversen *et al.*, 1990). Bicalutamide is replacing flutamide for this purpose, because it appears to have less hepatotoxicity and needs to be taken only once a day instead of three times a day. Flutamide also has been used to treat hirsutism in women, and it appears to be as effective as any other treatment (Venturoli *et al.*, 1999), but its hepatotoxicity cautions against its use for this cosmetic purpose.

Spironolactone. Spironolactone (ALDACTONE; *see* Chapter 29) is an inhibitor of aldosterone which also is a weak inhibitor of the androgen receptor and a weak inhibitor of testosterone synthesis. When it is used for treatment of fluid retention or hypertension in men, gynecomastia is a common side effect (Caminos-Torres *et al.*, 1977). Conversely, it can be used intentionally in women to treat hirsutism, for which it is approved by the U.S. Food and Drug Administration and is moderately effective (Cumming *et al.*, 1982), but it may cause irregular menses. **Cyproterone Acetate.** Cyproterone acetate is a progestin and a weak antiandrogen by virtue of binding to the androgen receptor. It is moderately effective in reducing hirsutism alone or in combination with an oral contraceptive (Venturoli *et al.*, 1999), but it is not approved for use in the United States.

Selective Androgen-Receptor Antagonists. A group of quinoline derivatives has been developed that act as antagonists at the androgen receptor in rat prostate glands but not in the pituitary. Analogous effects have not yet been demonstrated in human beings, but these compounds suggest the possible development of selective androgen-receptor antagonists.

5 α -Reductase Inhibitors. *Finasteride* (PROSCAR) is an antagonist of 5 α -reductase, especially the type II, so it blocks the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia. It was developed as a treatment for benign prostatic hyperplasia, and it is approved in the United States and many other countries for this purpose. When it is administered to men with moderately severe symptoms due to obstruction of urinary tract outflow, serum and prostatic concentrations of dihydrotestosterone decrease, prostatic volume

decreases, and urine flow rate increases (McConnell *et al.*, 1998). Impotence is a well-documented although infrequent side effect of this use, although the mechanism is not understood. *Finasteride* also is approved for use in the treatment of male pattern baldness under the trade name PROPECIA, even though that effect is presumably mediated via the type I enzyme. It appears to be as effective as flutamide and the combination of estrogen and cyproterone in the treatment of hirsutism (Venturoli *et al.*, 1999), but is not approved in the United States for this purpose.

For further discussion of disorders of the testes and of sexual differentiation, see Chapters 336 and 339 in *Harrison's Principles of Internal Medicine*, 14th ed., McGraw-Hill, New York, 1998.

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MONOGRAPHS AND REVIEWS

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